

# EXPERT OPINION

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## Conquests and perspectives of cardio-oncology in the field of tumor angiogenesis-targeting tyrosine kinase inhibitor-based therapy

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**Introduction:** Angiogenesis is fundamental for tumor development and progression. Hence, anti-angiogenic drugs have been developed to target VEGF and its receptors (VEGFRs). Several tyrosine kinase inhibitors (TKIs) have been developed over the years and others are still under investigation, each anti-VEGFR TKI showing a different cardiotoxic profile. Knowledge of the cardiac side-effects of each drug and the magnitude of their expression and frequency can lead to a specific approach.

**Areas covered:** This work reviews the mechanism of action of anti-VEGFR TKIs and the pathophysiological mechanisms leading to cardiotoxicity, followed by close examination of the most important drugs individually. A literature search was conducted on PubMed selecting review articles, original studies and clinical trials, with a focus on Phase III studies.

**Expert opinion:** Side-effects on the cardiovascular system could lead both to the worsening of general health status of cancer patients and to the discontinuation of the cancer treatment affecting its efficacy. Cardiologists often have to face new triggers of heart disease in these patients. They need a specific approach, which must be carried out in cooperation with oncologists. It must start before cancer treatment, continue during it and extend after its completion.

**Keywords:** axitinib, cardio-oncology, cardiotoxicity, pazopanib, regorafenib, sorafenib, sunitinib, tyrosine kinase inhibitors, vandetanib, VEGF

*Expert Opin. Drug Saf. [Early Online]*

### 1. Introduction

For many years cancer research has aimed to find new therapeutic options that could go beyond, and substitute, the already existing chemotherapy drugs in tumor treatment, so as to limit side-effects and overcome the edge of the treatment used. Therefore, in the past years, new targeted drugs that have a specific molecular target have been developed. Among the therapeutic agents which are now under development in oncology, angiogenic process is one of the main targets. These anti-angiogenic drugs act on the development of new blood vessels that furnish an adequate metabolic contribution to the microenvironment, which is necessary for tumor growth and its systemic spread [1]. In this review, we discuss the anti-angiogenic drugs targeting tyrosine kinase receptors approved by the FDA: sorafenib (2005), sunitinib (2006), pazopanib (2009), vandetanib (2011), axitinib (2012) and regorafenib

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**Article highlights.**

- The angiogenic process is a physiological one based on the equilibrium between pro-angiogenic (such as VEGF, which regulates endothelial cells) and anti-angiogenic molecules.
- VEGF-A is the main isoform, which is involved in cell migration, proliferation and survival.
- VEGF signaling suppression, through the impairment of nitric oxide synthesis, determines endothelial dysfunction and vasoconstriction, producing a state of non-perfusion, which are reasons for hypertension and microvascular rarefaction.
- Platelet-derived growth factor receptor- $\beta$  is important for adaptation to afterload stress in cardiomyocytes; indeed its suppression determines a reduction in cardiac capillary density and local tissue hypoxia, playing a role in the worsening of ventricular hypertrophy, ventricular dilation and heart failure.
- Each tyrosine kinase inhibitor exerts different cardiotoxicity (there are two types of toxicity: on-target toxicity, also called target-related, and off-target toxicity) on the heart and the cardiovascular system through side-effects that have different magnitudes of expression and frequencies.
- The recent and developing drugs seem to produce less cardiotoxicity compared to the older molecules, and this applies especially to nintedanib.

This box summarizes key points contained in the article.

(2012). Besides, we discuss two other drugs which have not yet been approved. These drugs are vatalanib and nintedanib (Table 1).

## 2. Mechanism of action of anti-VEGFR tyrosine kinase inhibitors

The angiogenic process starts on the basis of a balance in the action of several regulatory molecules that could stimulate or inhibit the growth. These regulatory molecules include: VEGF, acidic fibroblast growth factor (FGF), basic FGF, TGF- $\alpha$ , TGF- $\beta$ , hepatocyte growth factor (HGF or scatter factor), TNF- $\alpha$ , angiogenin, angiostatin, IL-8 and the angio-poietins [2]. VEGF is a growth factor that acts specifically on endothelial cells. It regulates their activity, being crucial in angiogenesis both physiologically and pathologically. VEGF can occur in various isoforms, including VEGF-A, VEGF-B, VEGF-C and VEGF-D. VEGF-A is a proangiogenic factor that plays important roles in cell migration, proliferation and survival. Alternative splicing yields at least six isoforms of VEGF-A, through a different incorporation of exons that determine the degree of cell surface and extracellular matrix association. These isoforms are respectively constituted by 121, 145, 165, 183, 189 and 206 amino acid residues. The VEGF165 is the predominant form. These growth factors bind to VEGF receptors on endothelial cells and promote their proliferation, survival, migration and tube formation.

These isoforms in turn interact with receptor tyrosine kinases (RTKs) that present three forms: VEGFR1, VEGFR2 and VEGFR3. VEGF binds with higher affinity to VEGFR1 than to VEGFR2, the latter having a stronger tyrosine kinase activity. Besides, VEGFR2 is widely assumed to be the mediator of the pro-angiogenic activities of VEGF. VEGFR3 is involved in lymphangiogenesis and does not bind VEGF-A [2-4]. Nevertheless, VEGFR1 and VEGFR2 could crosstalk inter- and intra-molecularly. VEGF binds to the VEGFR, leading to receptor dimerization and subsequent autophosphorylation of this complex. The phosphorylated receptor interacts with a variety of cytoplasmic signaling molecules, leading to signal transduction and eventually angiogenesis. The classical Ras/Erk and PI3K/Akt-dependent pathways are involved in the signaling activated by the VEGF-VEGFR network, thus leading to the proliferation and survival of endothelial progenitors [4]. There are three classes of PI3Ks grouped according to structure and function. Class IA PI3Ks are activated by growth factor (such as VEGF) stimulation through RTKs. The regulatory subunit, p85, directly binds to phosphotyrosine residues on RTKs and/or adaptors. This bond relieves the intermolecular inhibition of the catalytic subunit, p110, by p85 and localizes PI3K to the plasma membrane where resides its substrate, phosphatidylinositol 4,5-bisphosphate (PI[4,5]P2). PI3K can also be stimulated by activated Ras. Additionally, the p110 $\beta$  catalytic subunit can be activated by G-protein coupled receptors. PI3K phosphorylates PIP2 (Phosphatidylinositol 4,5-bisphosphate) on the 3'OH position to produce PI(3,4,5)P3. PI(3,4,5)P3 brings two PH domain-containing serine/threonine kinases, phosphoinositide-dependent kinase 1 (PDK1) and AKT, into close proximity. PDK1 activates AKT by phosphorylating it at threonine 308. PI3K-AKT signaling promotes cell growth and survival by several mechanisms. AKT promotes cell survival by inhibiting proapoptotic Bcl-2 family members. AKT also impedes negative regulation of the transcription factor NF- $\kappa$ B, leading to increased transcription of antiapoptotic and prosurvival genes. Phosphorylation of Mdm2 by AKT antagonizes p53-mediated apoptosis [5]. The recognition of the VEGF pathway as a key regulator of angiogenesis has led to the development of several VEGF-targeted agents that include: neutralizing antibodies to VEGF or VEGFRs, soluble VEGF receptors or receptor hybrids and tyrosine kinase inhibitors (TKIs) with selectivity for VEGFRs. TKIs are more selective rather than specific for a particular kinase, in relation to their course of action at the ATP-binding pocket. So, TKIs are designed to target VEGF receptors, but they are actually 'multi-kinase' inhibitors. For example, sorafenib and sunitinib also have significant activity against the Raf, platelet-derived growth factor receptor (PDGFR $\beta$ ), fibroblast growth factor receptor (FGFR), FLT3, KIT and FMS (also known as CSF1R) receptors. Therefore, it is likely that some of the clinical activity can be attributed to activity on other tyrosine kinase receptors. Particularly, some VEGFR-targeted TKIs significantly inhibit

**Table 1. Angiogenesis tyrosine kinase inhibitors: year of FDA approval, labels, pivotal trials.**

Drug	FDA approval (year)	Approved for	Phase III trials	Authors
Sorafenib	2005	Hepatocellular carcinoma Child-Pugh A or B mRCC	SHARP trial Asia-Pacific trial (NCT00492752) TARGET trial	Llovet <i>et al.</i> (2008) [32] Cheng <i>et al.</i> (2009) [36] Escudier B <i>et al.</i> (2009) [34]
Sunitinib	2006	Metastatic GIST mRCC Pancreatic neuroendocrine tumors	NCT00075218 NCT00098657 and NCT00083889 NCT00428597	Demetri <i>et al.</i> (2006) [39] Motzer <i>et al.</i> (2007) [40] Raymond <i>et al.</i> (2011) [41]
Pazopanib	2009	Relapsed or refractory RCCs Soft-tissue sarcomas	VEG105192 (NCT00334282) PALETTE trial	Sternberg <i>et al.</i> (2010) [49] van der Graaf <i>et al.</i> (2012) [51]
Vandetanib	2011	Metastatic medullary thyroid carcinoma	NCT00410761	Wells <i>et al.</i> (2012) [57]
Axitinib	2012	Second-line treatment of patients with mRCC	AXIS trial NCT00920816	Rini <i>et al.</i> (2011) [62] Hutson <i>et al.</i> (2013) [65]
Regorafenib	2012	Advanced GIST Previously treated metastatic colorectal cancer	GRID trial CORRECT trial	Demetri <i>et al.</i> (2013) [70] Grothey <i>et al.</i> (2013) [71]
Vatalanib	Not approved yet	–	CONFIRM 1 trial (NCT00056459) CONFIRM 2 trial	Hecht <i>et al.</i> (2011) [75] Van Cutsem <i>et al.</i> (2011) [76]
Nintedanib	Not approved yet	–	LUME-Lung 1	Reck <i>et al.</i> (2014) [83]

GIST: Gastrointestinal stromal tumor; mRCC: Metastatic renal cell carcinoma.

the activity of PDGFRs, and this leads to a dual attack on the vasculature (VEGFR on endothelial cells and PDGFR on pericytes). For this reason, it shows, in preclinical studies, a greater efficacy than inhibiting a single receptor family [6].

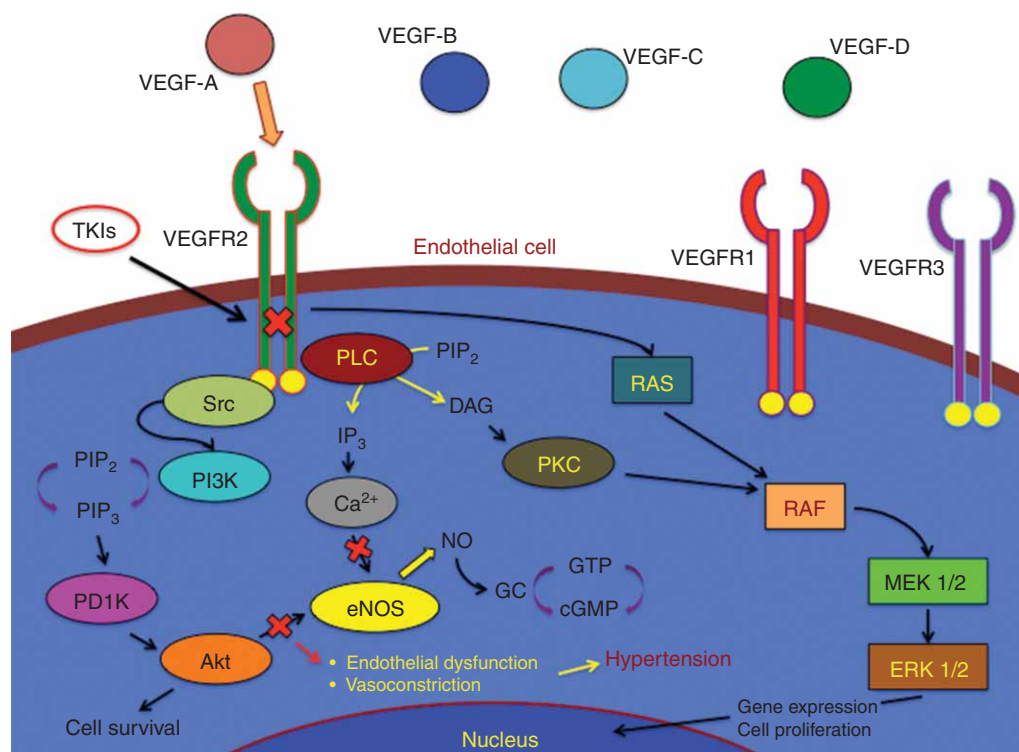
### 3. Pathophysiological mechanisms of cardiotoxicity of anti-angiogenic drugs

TKIs inhibit TK receptors both in cancer and normal cells. Therefore, this action on normal tissues explains their side-effects. The most common side-effects include diarrhea and skin rash. Although cardiac toxicity is less common, it is more serious and difficult to diagnose in early stages. Cardiac toxic effects of TKIs include asymptomatic QT prolongation, reduction in left ventricular ejection fraction (LVEF), symptomatic congestive heart failure (CHF), hypertension, acute coronary syndromes (ACS) and myocardial infarction (MI). Sudden death has also been associated with these drugs. Not all TKIs exert the same toxicity on the heart muscle and the cardiovascular system. The level of expression of certain TK receptors in the cardiomyocytes does not correlate with the toxicity induced by their related inhibitors; rather the function of a specific TK receptor constitutes the determining factor for the cardiac effects of its inhibition. The exact rates of cardiotoxicity are not well known yet.

The inhibition of the ‘key’ kinases that drive tumorigenesis could potentially compromise the survival of cardiomyocytes, leading to the cardiotoxicity exerted by TKIs. This toxicity can be distinguished into two types: 1) on-target toxicity, also known as mechanism-based or target-related, in which the kinase that is targeted in the cancer also provides an

important maintenance function in the heart and vasculature. Thus, the inhibition leads to adverse consequences in the heart. 2) Off-target toxicity: a kinase that was not intended to be inhibited by a drug is inhibited, and if this kinase plays a key role in the heart its inhibition will lead to cardiotoxicity. Off-target toxicity is inherently related to the limited selectivity of most TKIs. In fact, cardiotoxicity results from the non-specific inhibition of multiple kinases on signaling pathways important for maintaining ventricular function. The inhibition by sunitinib on AMPK (AMP-activated protein kinase) is an example of off-target toxicity. This kinase plays key roles in maintaining metabolic homeostasis in the heart, especially in the setting of energy stress. AMPK is activated when energy stores drop in the cardiomyocyte. It leads to increased energy generation and decreased energy utilization, but it is not activated in the energy-stressed cardiomyocytes. AMPK activity is reduced in sunitinib-treated heart models and in cultured cardiomyocytes. This drug causes cell damage, so that there is a myocardial cell loss, or inhibits normal repair processes [7-13]. It has to be specified that AMPK inhibition is not the only one responsible for cardiotoxicity and it could be only partial. Indeed, metformin, which is able to activate AMPK in myocytes, did not defend them from sunitinib-induced toxicity [14].

The inhibition of VEGF signaling by TKIs can cause hypertension, and this is one of the main cardiac toxic effects (Figure 1). VEGF, through VEGFR2, has a hypotensive effect. In normal cells, functional VEGFR2 triggers PI3K, through Src, and phospholipase C (PLC). PI3K converts PIP<sub>2</sub> to PIP<sub>3</sub>. The latter acts on PD1K, which initiates Akt. So in the end, Akt stimulates the endothelial nitric oxide synthase



**Figure 1.** The effects of angiogenesis tyrosine kinase inhibitors on hypertension. The block of VEGFR function induces changes in eNOS pathway with consequences on vasoconstriction and endothelial dysfunction and subsequently on hypertension.

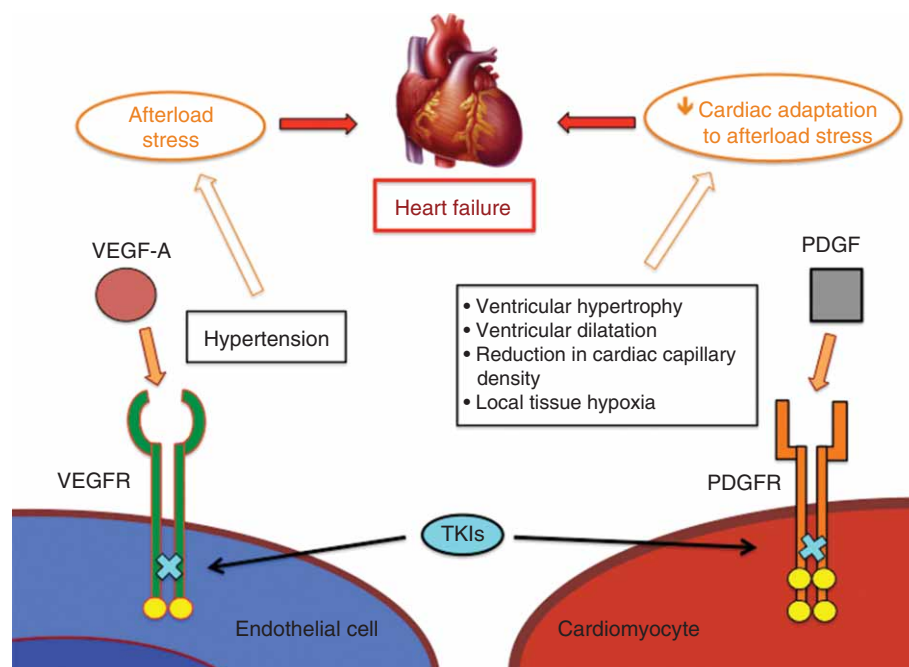
DAG: Diacylglycerol; eNOS: Endothelial nitric oxide synthase; PLC: Phospholipase C; TKIs: Tyrosine kinase inhibitors.

(eNOS). On the other hand, activated PLC transforms  $PIP_2$  in the second messengers, inositol trisphosphate ( $IP_3$ ) and diacylglycerol. The first of these two products leads to the entry of  $Ca^{2+}$  ions within the cell. The enhanced concentration of calcium starts eNOS activity. Hence, both of these two pathways lead to the upregulation of eNOS. eNOS determines the production of nitric oxide (NO), which regulates vascular relaxation. In fact, NO activates guanylyl cyclase that raises cGMP levels, determining vasodilation, reducing smooth muscle cells growth and platelet aggregation. Therefore, the elimination of constitutive baseline VEGF signaling induces endothelial dysfunction and vasoconstriction. These events occur because the activity of the inducible NO synthesis is compromised. These two events create a state of non-perfusion. Hence, these are the bases for hypertension and microvascular rarefaction, which means the extinction of the small blood vessels that constitute the microcirculation. In fact, the depletion of VEGF-A release, in protracted hypoxic conditions, is considered an important factor, which contributes to decompensated heart failure. In the advanced stage of the disease, VEGF-A reduction has been connected to unbalanced microvascular growth and reduced capillary density. VEGF is upregulated during hypertension, providing compensatory responses. Anti-VEGF therapy suppressing it determines a weaker compensatory role. Hypertension is associated with the development of left ventricular hypertrophy, which is

a strong independent predictor of cardiovascular morbidity and mortality. Hypertensive cardiac remodeling results in cardiomyocyte hypertrophy outgrowing capillary expansion. The decline in microvascular density leads to hypertension-associated cardiovascular events. Animal models with cardiomyocyte-specific deletion of the VEGF gene had fewer coronary microvessels, thinned ventricular walls and depressed contractile function. Induced hypertrophy in VEGF-deficient mice expedite the transition from compensatory hypertrophy to failure. In other animal models, data enlightened that supplementation of VEGF, during prolonged pressure overload, preserved the contractile function. However, it has to be specified that the decrease in microvascular density is not the only reason for cardiovascular events. Other important factors play a key role in the development of load-induced cardiac pathologies, which are abnormal  $Ca^{2+}$  handling in cardiomyocytes, a shift in energy metabolism and accumulation of interstitial fibrosis.

Some studies demonstrated that another participant in the TKI-induced hypertension could be endothelin (ET). The administration of sunitinib showed an increase in circulating ET-1 levels, prompting that the ET pathway plays an important role in sunitinib-induced increase of blood pressure. ET-1 carries out a vasoconstrictor effect through the activation of NADPH (which is the reduced form of nicotinamide adenine dinucleotide phosphate) oxidase and the generation





**Figure 2.** The role of the inhibition of main angiogenesis mediators, VEGFR and PDGFR, in the development of heart failure through afterload stress.

PDGFR: Platelet-derived growth factor receptor; TKIs: Tyrosine kinase inhibitors.

of reactive oxygen species. Vasoconstriction determines hypertension, which has also been related to an increase in reactive oxygen species. Besides, ET-1 has been shown to promote angiogenesis in cancer. Therefore, the use of ET-1 receptor antagonists could be important for treatment. Studies in animals demonstrated that the coadministration of an ET-1 receptor antagonist with an RTKI limited blood pressure enhancement.

The deletion of the PDGFR- $\beta$  gene in cardiomyocytes causes in models next to afterload stress a worsening of ventricular hypertrophy, ventricular dilation and heart failure, demonstrating how it is crucial for adaptation to afterload stress. It leads also to a reduction in cardiac capillary density and evidence of local tissue hypoxia. As regards heart failure, another main cardiac toxic effect, an hypothesis has been proposed to explain how anti-angiogenic drug treatment can lead to it. This hypothesis considers two aspects. The first one is the development of hypertension, which leads to afterload stress on the heart. Normally, the heart is able to adapt to afterload stress through compensatory mechanisms, but the inhibition of PDGFR- $\beta$ , determined by anti-angiogenic TKIs, inhibits cardiac adaptation to afterload stress. Hence, it causes heart failure (Figure 2) [15-23]. Common side-effects are peripheral edema, an indicator of cardiac dysfunction, and symptoms like fatigue and dyspnea that could also be attributed to the disease itself or they could be associated with other conditions [9]. If on one hand, these studies on animal models showed the role of the PDGFR- $\beta$  in

cardiomyocytes, on the other hand the recent study by Chintalgattu *et al.* revealed that the pericyte is the principal cell involved in coronary microvascular abnormalities and cardiac dysfunction caused by sunitinib. They showed that sunitinib-induced cardiotoxicity is linked to a decrease of coronary microvascular pericytes, which determines changes in the coronary microvasculature. Besides, they disclosed that the effect of sunitinib is specifically direct on pericytes of the cardiac muscle [24].

Among the main cardiac side-effects linked to TKIs are thromboembolic events. In normal conditions, VEGF-receptor signaling determines, in endothelial cells, an increase of the prosurvival factor Bcl-2 and modulation of the MAPK pathway, which is involved in a variety of cellular functions. Bcl-xL is also an anti-apoptotic cell-survival factor. In endothelial cells, it up-regulates VEGF-A production, and in platelets, it is a major determinant of the life span. VEGF-A-induced signaling, through VEGFR2, directly regulates the junctional machinery in the intercellular gaps. VEGF-A alters the endothelial-cell phenotype by increasing vascular permeability, up-regulating expression of urokinase, tissue plasminogen activator and the vascular cell adhesion molecule. The cytoplasmic domain of VEGFR2 is part of a macromolecular complex. Shear stress enhances the formation of this complex, thereby converting the adherens junction into a mechanical transducer that initiates 'outside-inside' signaling. Megakaryocytes and platelets contain the three major isoforms of VEGF-A – VEGF121, VEGF165 and VEGF189

– that are released after exposure to thrombin. VEGF secreted by one or more cells, both in a paracrine and in an autocrine way, activates VEGFR2, inducing its phosphorylation and activation. The autocrine loop keeps vascular permeability stabilizing the complex for the normal steady-state of the endothelial function, while the paracrine pathway seems to play a key role in promoting vascular permeability in the non-steady states, such as inflammation and disassembling the complex. Paracrine stimulation is necessary for vasculogenesis in the angiogenesis of cancer or inflammation. Paracrine VEGF-A, delivered to the vascular lining by platelets and other cells, increases endothelial cell production of Bcl-2, and platelet-activating factor, a phospholipid pro-inflammatory mediator, induces expression of VEGF-A by endothelial cells. Another contributor to microvascular stability is Bcl-xL. When Bcl-xL and Bcl-2 are decreased, due to a reduction in VEGF levels during anti-VEGF drug treatment, there is an imbalance between cell survival and apoptosis. Endothelial cell apoptosis leads to an exposure of the subendothelial membrane that activates the coagulation cascade. This event promotes thromboembolic events. Besides, VEGF released from platelet upregulates components of the fibrinolytic system, and so anti-VEGF drugs have an adverse effect on this mechanism [25-30].

## 4. Drugs formerly approved for cancer treatment

### 4.1 Sorafenib

Sorafenib is a small molecule, an oral inhibitor of multiple kinases that are present in tumor cells and tumor blood vessels. It potently inhibits several of both serine/threonine and tyrosine kinases including VEGFR2 and VEGFR3, PDGFR $\alpha$  and PDGFR $\beta$ , c-KIT, FLT3, RAF1 (v-raf-1 murine leukemia viral oncogene homolog 1) and BRAF kinases (v-raf murine sarcoma viral oncogene homolog B1), including BRAF<sub>V600E</sub>. It is currently registered for the treatment of advanced primary hepatocellular carcinoma (HCC) Child-Pugh A or B and advanced/metastatic renal cell carcinoma (mRCC). This drug is generally well tolerated. It has several side-effects, including cardiotoxicity. It is associated with cardiac ischemia or infarction and hypertension [31]. In sorafenib-treated patients, a higher incidence of hypertension, usually mild-to-moderate, has been observed. Besides, it occurs earlier than the other drugs, but on the other hand, it responds to standard anti-hypertensive therapy.

Sorafenib was studied in advanced HCC by Llovet *et al.* in a multicenter, randomized, double-blind, placebo-controlled, Phase III trial. This trial was conducted at 121 centers in 21 countries in Europe, North America, South America and Australasia. The authors enlisted 602 patients with advanced HCC who had not received previous systemic treatment. Among the sorafenib-treated patients (n = 297), any grade hypertension was present in 5%. Drug-related grade 3 hypertension was 2%, while there was no drug-related grade

4 hypertension. Cardiac ischemia or infarction was revealed, respectively, in 3% and 1% of patients [32,33].

In a Phase III study, sorafenib was administered in pre-treated patients affected by mRCC. The incidence of all-grade hypertension was 17% in comparison with the placebo group in which it was 2%. Grade 3 and grade 4 hypertension were recorded in 4% of the sorafenib-treated group versus 1% in placebo. Similar results were achieved in the expanded access program in North America, in which about 2,504 patients were enrolled. The incidence of all-grade hypertension was 12%, while grade 3 was present in 5%. Comparable results have also been obtained in a Phase III, randomized, double-blind, placebo-controlled trial, in which the authors analyzed the use of sorafenib in patients affected by HCC. Besides, it has been demonstrated that sorafenib determines a prolongation of the QT/QTc interval. This can lead to an increased risk of ventricular arrhythmias [34-36]. Retrospective analyses suggest that the development of hypertension, especially grade moderate-to-severe, can be associated with a greater efficacy of anti-angiogenic drugs. Ravaud *et al.* studied 93 patients evaluating the possible relationship between the onset of hypertension and the drug efficacy treating them with sunitinib, sorafenib and bevacizumab as first, second and third line for mRCC. It was shown that among patients who developed hypertension of grade 2 or higher, 88% had clinical benefit. Besides, 53% of these patients maintained the clinical benefit for a period  $\geq 6$  months [37].

Sorafenib treatment can determine an increased risk of developing heart disease. Escudier *et al.*, in their Phase III trial, in patients with mRCC, noticed that the incidence of heart attack or cardiac ischemia occurring during treatment was 4.9% in the sorafenib-treated group, while it was 1.4% in the placebo group. The incidence of CHF developed in patients with mRCC treated with sorafenib was 1.7% versus 0.7% in the placebo group [34]. Instead, in the expanded access program in North America, these type of cardiac events were not documented [35]. Cheng *et al.*, in their Phase III study, in patients with advanced HCC, observed that the incidence of heart attack or cardiac ischemia occurring during treatment was 2.7% in sorafenib-treated patients and 1.3% in the placebo-treated group. As regards the CHF, they had different results, if compared with the other studies, because they reported lesser events in sorafenib-treated patients (0.9%) than the placebo-treated group (1.1%) [36].

Finally, in a meta-analysis that included over 10,000 patients, the incidence of arterial thromboembolic events (ATEs) was analyzed. It was 1.7% for sorafenib-treated patients. The relative risk (RR) of ATEs for TKI in comparison with controls was of 3.03. RR for sorafenib was 3.1, and it was 2.39 for sunitinib [38].

### 4.2 Sunitinib

Sunitinib is a small molecule TKI. It inhibits mutated or over-expressed kinases in cancer cells. It acts on a number of growth factor receptors regulating both tumor cell

proliferation/survival and tumor angiogenesis including VEGFRs 1 – 3, PDGFR $\alpha$  and PDGFR $\beta$ , c-KIT, FMS-like tyrosine kinase-3 (FLT3), CFS-1 receptor (CSF1R) and the product of the human RET gene (RET). Currently, sunitinib is registered for the treatment of metastatic and unresectable gastrointestinal stromal tumor (GIST) [39], mRCC [40] and unresectable or metastatic well-differentiated pancreatic neuroendocrine tumors [41]. It is generally well tolerated. It has various side-effects, including cardiotoxicity [39,40,42]. Hypertension is the most common cardiovascular adverse event among sunitinib-treated patients. The rate and severity of hypertension vary according to the definitions of hypertension used and the population studied. In a meta-analysis including 13 clinical trials and a total of 4,999 patients, the incidence of all-grade hypertension was 21.6%. The incidence of hypertension warranting the addition or adjustment to dosing of more than one medication (NCI grade 3 or grade 4) was 6.8%. The RR of grade 3 or grade 4 hypertension using sunitinib compared to placebo was 23. Rini *et al.* using less strict criteria found that 81% of patients with mRCC treated with sunitinib developed systolic blood pressure higher than 140 mmHg and 67% developed diastolic blood pressure higher than 90 mmHg [43].

This drug, more than the other TKIs, can cause left ventricular dysfunction. Schmidinger *et al.* performed an observational study of mRCC patients treated with either sorafenib or sunitinib. They found that about one-third of the cohort developed a cardiac event, defined as increased cardiac enzymes, symptomatic arrhythmia requiring treatment, new left ventricular dysfunction or ACS. About 10% of the cohort required intermediate or intensive care admission [16]. Chu *et al.* conducted a review focusing on cardiac adverse events in 75 patients with imatinib-resistant, metastatic GIST treated with sunitinib, as part of an early Phase I/II clinical trial. The 11% of patients treated with sunitinib, developed cardiac adverse events (e.g., CHF, MI or cardiac death). The most common event was NYHA class III – IV CHF (8%). The treatment with the FDA-approved dosage showed a steady decrease in LVEF  $\geq 15\%$  of the EF. Of 36 patients, 4 developed either CHF or LVEF decline of  $\geq 20\%$  to an EF  $< 50\%$ . Sunitinib also induced significant blood pressure elevations; approximately 47% of the patients developed hypertension  $> 150/100$  mmHg. Grade 3 hypertension occurred in 17% of patients [44]. In an observational, single-center study, a total of 86 patients was treated with either sunitinib or sorafenib. A total of 74 patients were eligible for assessment of cardiotoxicity during TKI treatment. Among these patients, 25 (33.8%) experienced a cardiac event, 11 patients among sunitinib-treated and 14 among sorafenib-treated. The 40.5% had ECG changes including rhythm changes, conduction disturbances, axis change, QRS amplitude changes, ST segment depression and elevation, T wave changes and QT prolongation, 18% of these were symptomatic. Of 25 patients having cardiac events, 13 presented typical clinical symptoms, such as angina, dyspnea

and dizziness; 7 patients (9.4%) were seriously compromised and required intermediate care or intensive care admission. A total of 22 patients underwent echocardiograms at the event, and 10 of them were abnormal. Abnormalities included reduced LVEF in 9 patients, regional contractile dysfunctions in 7 and relaxation disturbances greater than grade 1 and pericardial effusion in 1 patient each. The median duration of TKI treatment on event occurrence was 8 weeks (ranging from 2 to 48 weeks). In all these studies, all patients recovered after cardiovascular management (e.g., medication, coronary angiography, pacemaker implantation and heart surgery) and were considered eligible for TKI continuation. Statistically, there was no significant survival difference between patients who experienced a cardiac event and those who did not experience a cardiac event. A noteworthy aspect is the high percentage of patients with increased cardiac biomarkers, such as creatine kinase myocardial band (CK-MB) and troponins, in the treatment group. Indeed, among the sunitinib-treated patients, 54.5% had abnormal CK-MB and troponin. An increased CK-MB was seen in 78.6% patients treated with sorafenib, while an abnormal troponin was seen in 21.4% [45].

### 4.3 Pazopanib

Pazopanib is an orally assumed multitarget angiogenesis inhibitor. It targets VEGF-1, VEGF-2 and VEGF-3 receptors, PDGF- $\alpha$  and PDGF- $\beta$  receptors, and c-KIT. It is used in the treatment of relapsed or refractory RCCs [46] and soft-tissue sarcomas. Recent Phase II and Phase III trials highlighted a possible use of this drug in the treatment of selected epithelial ovarian cancer patients [47]. Qi *et al.* in a meta-analysis showed that the average incidence of all-grade hypertension among patients receiving pazopanib was 35.9%. High-grade (grade 3 or grade 4) hypertension was associated with significant morbidity and subsequent dose reduction or discontinuation of pazopanib treatment. The trials reported an average incidence of high-grade hypertension among patients receiving pazopanib of 6.5% [48].

In a trial by Sternberg *et al.*, the authors showed that arterial thrombotic events occurred in 3% of pazopanib-treated patients, among these MI/ischemia 2%, cerebrovascular accident  $< 1\%$  and transient ischemic attack  $< 1\%$  compared with the placebo-arm, in which there were none [49]. Pazopanib can also induce electrocardiographic changes. QT-prolongation and torsade de pointes, though rare, are serious adverse event due to pazopanib therapy. Less than 2% of patients can have a prolonged QT interval while receiving pazopanib. Due to the gravity of this event, baseline and periodic electrocardiograms and electrolyte monitoring should be carried out. For this reason, an oncologist should pay more attention when pazopanib is used in patients with a history of QT prolongation or if they are using any other medication that may affect the QT interval [50].

The PALETTE trial studied pazopanib compared to placebo in angiogenesis inhibitor-naïve patients with metastatic soft-tissue sarcoma, who progressed despite previous standard

chemotherapy. In this study, fatigue and hypertension were among the most common adverse effects, with a G3 – 4 toxicity rate of 13 and 7%, respectively. LVEF dropped in 16 patients in the pazopanib group, compared to 3 in the placebo group, during or after treatment. Among these 16 patients, 3 were symptomatic. However, LVEF had improved in 8 patients. Among these, 5 continued pazopanib and 3 discontinued for other reasons [51].

#### 4.4 Vandetanib

Vandetanib (ZD6474) is an orally active small molecule TKI. It acts against the VEGFR2. It also has inhibitory activity at sub-micromolar concentrations against VEGFR3, the EGFR, Rearranged during Transfection (RET) tyrosine kinase, while it acts on VEGFR1 and PDGFR $\beta$  at micromolar concentrations. This drug has been approved for the treatment of adult patients with unresectable, locally advanced or metastatic medullary thyroid carcinoma [52-55]. Vandetanib is tolerable at doses of 300 mg or less. Wells *et al.* studied 331 patients with locally advanced or metastatic medullary thyroid cancer in a randomized, double-blind, Phase III trial. Among the 231 vandetanib-treated patients, any grade hypertension occurred in 32% and grade 3 or higher hypertension occurred in 9%. Asthenia of any grade arose in 14%, while grade 3 or higher was seen in 3%. Another adverse event was dyspnea, grade 3 or more, which was present in only 1%. QTc prolongation required dose reduction in 35% of the vandetanib-treated patients. About 18 patients (8%) developed protocol-defined QTc prolongation, grade 3 or higher, but there were no reports of torsades de pointes. Any grade QTc prolongation arose in 33 patients (14%). Among these cardiac adverse events, QTc prolongation is a noteworthy adverse effect. It has been proposed that potassium and magnesium deficiency, which is possibly secondary to diarrhea, have a role in its onset. The only adverse event leading to discontinuation of vandetanib was asthenia (1.7%). Five patients in the vandetanib arm experienced adverse events leading to death during the randomized phase; among these events there was respiratory arrest, respiratory failure, arrhythmia and acute cardiac failure in 1 patient [56,57]. Approximately similar results were obtained by Leboulleux *et al.* in a randomized, double-blind, Phase II trial. Any grade hypertension occurred in 34% of the vandetanib-treated patients. Any grade asthenia came about in 26%, while grade  $\geq 3$  asthenia in 7%. Any grade QTc prolongation was present in 23%, while grade  $\geq 3$  QTc prolongation in 14%. Grade  $\geq 3$  dyspnea ensued in 3%. Among the most common adverse events leading to discontinuation of vandetanib was QTc prolongation in 5 patients (7%). They noted no cardiac complications linked to the prolongation of the QTc [58].

These data were analyzed together with other trials in a meta-analysis by Qi *et al.* They included a total of 11 trials with 3,154 patients affected by metastatic thyroid cancer (MTC), NSCLC and other malignancies. The average incidence of all-grade hypertension among patients receiving

vandetanib was 24.2%. Among the 11 trials, 8 reported a mean incidence of 6.4% for high grade hypertension. The mean all-grade and high grade incidences of hypertension in patients with non-MTC/NSCLC tumors were 15.4 and 3.4%, respectively. Besides, the incidence about all-grade and high grade hypertension in non-MTC/NSCLC tumors were lower than NSCLC, in which it was 21.8% for all-grade hypertension and 7.6% for high grade hypertension and MTC. There was a significant difference between MTC and NSCLC in terms of the incidence of vandetanib-associated all-grade hypertension (RR 1.48), but not high grade hypertension. Finally, vandetanib was associated with a significantly increased risk of all-grade hypertension in comparison with non-MTC/NSCLC tumors, but not high grade hypertension [59]. In a meta-analysis by Zang *et al.*, the authors analyzed the incidence and risk of QTc interval prolongation by vandetanib in the cancer patient. This meta-analysis was based on 9 trials and included 2,188 patients. They showed that the overall incidence of all-grade and high-grade QTc interval prolongation was 16.4% and 3.7%, respectively, among patients with non-thyroid cancer, and 18.0% and 12.0%, respectively, among patients with thyroid cancer. If compared with the incidence of prolonged QTc interval determined by other drugs, the incidence of all-grade QTc interval prolongation associated with vandetanib is moderate. This is an important aspect because QTc interval prolongation is one of the most important risk factors that induce life-threatening consequence [60].

#### 4.5 Axitinib

Axitinib is a third-generation VEGFR inhibitor. It is highly selective and very potent for VEGFR1 – 3. It has been approved for use in the second-line treatment of patients with metastatic RCC after failure of prior treatment with sunitinib or a cytokine [61]. It has been studied in the AXIS trial (Phase III), in which axitinib was compared to sorafenib. The most common adverse events leading to discontinuation in the axitinib group were fatigue (1%; 4) and transient ischemic attack (< 1%; 3). The most frequent cardiovascular adverse event associated with axitinib was hypertension, occurring in > 30% of patients. Indeed, all-grade hypertension showed a frequency of 40%, while grade 3 or higher had a frequency of 16%. However, this study had several important limitations; mostly it was not a blinded trial. Further data revealed that diastolic blood pressure of 90 mmHg or higher during study can help predict axitinib efficacy in patients with solid tumors, including RCC [62,63]. In a meta-analysis by Qi *et al.*, the authors identified ten studies, including two Phase III trials and eight Phase II trials, for a total of 1,908 patients. The underlying malignancies for these trials included metastatic RCC, metastatic melanoma, metastatic breast cancer, advanced NSCLC, pancreatic cancer and all histological subtypes of advanced thyroid cancer. In each of these trials, hypertension was not described as a pre-existing condition. The mean incidence of all-grade hypertension



among patients receiving axitinib was 40.1%. As regards high grade (grade 3 or grade 4) hypertension, it was associated with significant morbidity, leading to dose reduction or discontinuation of axitinib. All the ten trials showed a mean incidence of high grade hypertension of 13.1% among those patients assuming axitinib. To investigate the role of axitinib in the development of hypertension and exclude the influence of other factors such as underlying malignancy, the authors calculated the RR of axitinib-induced hypertension. Treatment with axitinib increased the risk of developing all-grade hypertension, RR was 3.00. As regards high grade hypertension, RR was 1.71 [64].

In a recent randomized, open-label, Phase III trial by Hutson *et al.*, the most frequent all-grade, all-causality cardiovascular adverse event with axitinib was hypertension. The most frequently reported grade 3 or grade 4 cardiovascular adverse events were hypertension and asthenia in axitinib-treated patients. All-grade hypertension had an incidence of 49% (in 92 patients), while grade 3 hypertension had an incidence of 13% (25 patients) and grade 4 < 1% (1 patient). As regards asthenia, the incidence was 21% (39 patients) for all grades, 7% (13 patients) for grade 3 and 2% (3 patients) for grade 4. The most common all-causality serious cardiovascular adverse events were pleural effusion 2% (3 patients) and cardiac arrest 2% (3 patients) in the 189 patients in the axitinib-treated patients. Serious treatment-related adverse events included atrial flutter, cardiac arrest, MI, asthenia, aorto-duodenal fistula and hypertensive crisis < 1% each (1 patient). Besides, 1 patient in the axitinib group died of treatment-related cardiac arrest [65].

#### 4.6 Regorafenib

Regorafenib (BAY 73-4506) is an oral multikinase inhibitor targeting angiogenic, stromal and oncogenic RTKs with potent antitumor activity. It potently inhibits various sets of kinases, including the angiogenic and stromal RTKs VEGFR1-3, TIE2, FGFR1 and PDGFR- $\beta$ , which promote tumor neovascularization, vessel stabilization and lymphatic vessel formation and play an important role in the tumor microenvironment. They all contribute to tumor development and metastasis formation. Regorafenib also inhibits the oncogenic RTKs, KIT and RET, along with the intracellular signaling kinases c-RAF/RAF-1, BRAF and its V600E mutant form [66]. Regorafenib was approved for advanced GIST that cannot be surgically removed and no longer responds to imatinib and sunitinib, and for previously treated metastatic colorectal cancer [67-69].

In the GRID trial, an international, multicenter, prospective, randomized, placebo-controlled, Phase III trial, regorafenib has been studied in patients affected by advanced GISTs which failed to respond to imatinib and sunitinib. In this study, 240 patients were screened and 199 were randomized to receive regorafenib (133 patients) or placebo. The most commonly reported regorafenib-related adverse events of grade 3 or higher was hypertension. It was present in 31 of

132 patients (23.5%), and similar to other therapies targeting the VEGF/VEGFR pathway, is likely related to anti-angiogenic effects. Besides, hypertension was one of the most common drug-related adverse events of any grade in the regorafenib group, together with hand-foot skin reaction and diarrhea. Any grade hypertension was present in 64 patients (48.5%), grade 3 hypertension in 30 patients (22.7%), while grade 4 hypertension was reported in 1 patient (0.8%). This adverse event could be managed with dose modification and appropriate anti-hypertensive intervention. Grade 5 adverse events were reported in 7 (5.3%) of the 132 patients in the regorafenib group and in 3 (4.5%) of the 66 patients in the placebo group. In 3 patients, the grade 5 adverse events were considered by the investigators to be drug-related. Among these 3 patients, 1 in the regorafenib group had cardiac arrest [70]. Regorafenib has been studied in monotherapy in the CORRECT (Phase III) trial involving 114 centers in 16 countries in North America, Europe, Asia and Australia. Patients were enrolled when they had proven histological or cytological adenocarcinoma of the colon or rectum, who previously were treated with irinotecan- and oxaliplatin-based regimens. A total of 1,052 patients were screened in the study and 760 patients were randomized to receive regorafenib (505 patients) or placebo. Among these patients, 753 initiated treatment (regorafenib = 500). Any grade hypertension was reported in 139 among 500 patients treated with regorafenib (28%). The most frequent regorafenib-related cardiovascular adverse event of grade 3 was hypertension, affecting 36 patients (7%). Grade 4 hypertension was not reported. Another cardiovascular adverse event reported was dyspnea. Any grade dyspnea affected 28 patients (6%). Only 1 patient had grade 3 dyspnea (< 1%), while grade 4 dyspnea, also in this case, was not related [71,72].

### 5. New weapons in the fighting of cancer and tumor angiogenesis: developing drugs

#### 5.1 Vatalanib

Vatalanib (PTK787/ZK 222584) is an oral TKI that blocks the signaling pathway, acting competitively on the ATP-binding site of all three isoforms of VEGFR, VEGFR1 (Flt-1), VEGFR2 (KDR) and VEGFR3 (Flt-4). It also inhibits KIT and PDGFR $\alpha$  [73,74].

There are two important Phase III trials that studied patients affected by metastatic colorectal adenocarcinoma. The first one is the CONFIRM 1 trial, in which patients were randomly assigned to receive vatalanib plus FOLFOX4 or placebo plus FOLFOX4. The cardiovascular adverse events noticed by the authors were hypertension, which was present in 133 patients (23.0%); pulmonary embolism, which was present in 33 patients (5.7%); and deep vein thrombosis, which was observed in 30 patients (5.2%). All of these adverse events were grade 3 or grade 4. The most notable differences between the vatalanib group and the placebo group were for hypertension (23.0 vs 6.8%, respectively) and pulmonary

embolism (5.7 vs 1.7%, respectively) [75]. In the sister trial CONFIRM 2, 949 patients were screened and 855 patients were randomly assigned to receive vatalanib plus FOLFOX4 or placebo plus FOLFOX4. The recruited patients had previously treated mCRC, whose disease had recurred or progressed during or within 6 months of treatment with irinotecan in combination with a fluoropyrimidine. A higher percentage of patients in the vatalanib group than the placebo group experienced grade 3 or grade 4 hypertension, deep vein thrombosis, pulmonary embolism and thromboembolic events. Likewise, all-grade thromboembolisms. All-grade hypertension was present in 123 patients (29.1%), and 92 patients had grade 3 or grade 4 hypertension (21.8%). It was managed with vasodilation therapy. All-grade asthenia was also observed; it was present in 110 patients (26.1%), 30 patients had grade 3 or grade 4 asthenia (7.1%) [76].

Further trials have been conducted over the past years. A Phase II trial studied the use of vatalanib administered orally, daily, as second-line monotherapy in relapsed or documented progressing patients refractory to one prior first-line platinum-based chemotherapy or combined chemo-radiotherapy regimen, with proven stage IIIB or IV NSCLC. The authors noticed all-grade asthenia in 19%, and among these, grade 1 – 2 asthenia was present in 17% and grade 3 asthenia in 2%. As regards all-grade hypertension, it was present in 16%, grade 1 – 2 hypertension in 4% and grade 3 in 12%. Instead, pulmonary embolism showed lower percentages, with all grades being present in 5%, mainly grade 4. Additionally, two patients in the study died, possibly due to treatment-related pulmonary hemorrhage [77]. An open-label, Phase II, multicenter trial investigated the efficacy and tolerability of vatalanib in patients with metastatic or advanced pancreatic cancer who failed first-line gemcitabine-based therapy. The most common adverse events were grade 3 or grade 4, which included hypertension. It was reported in 20% [78].

## 5.2 Nintedanib

Nintedanib (BIBF 1120) is a new, potent, orally assumed triple angiokinase inhibitor. It can specifically inhibit all subtypes of VEGF, FGF and PDGFR $\alpha$  and  $\beta$ , together with RET and FLT3. It has an acceptable general safety profile, rare reports of hypertension or thromboembolic events and is usually well tolerated. Nintedanib is currently under investigation for the treatment of several solid tumor types, and among these, there are RCC, HCC, ovarian/endometrial cancer, lung cancer, breast cancer, prostate cancer, gliomas and colorectal cancer, due to its good tolerability. In a Phase II study, the efficacy and safety of nintedanib in comparison with sunitinib in patients with advanced RCC was evaluated. Nintedanib did not have a clinically significant effect on QTcF or uncorrected QT interval. Besides, it was not reported adverse events linked to the cardiovascular system. Patients did not develop adverse events that led to dose reduction or discontinuation of the drug; besides, no deaths were reported in association with drug-related serious adverse

events [79]. Nintedanib has been studied as a single agent, but also in combination with standard chemotherapeutic regimens. It was used in combination with pemetrexed to treat recurrent or advanced NSCLC patients previously treated with at least one line of platinum-based therapy or in combination with carboplatin/paclitaxel in patients with untreated advanced NSCLC. The only reported cardiac adverse event was hypertension, grade 1 or grade 2, in 15.4% of the patients. The toxicities of this agent are apparently acceptable, though the number of patients included in the Phase I and Phase II trials is still too small to obtain meaningful results about efficacy and safety [80,81]. It was also studied in a Phase II trial of maintenance therapy after chemotherapy for relapsed ovarian cancer by Ledermann *et al.* In this trial the authors observed only deep vein thrombosis (1 patient) and hypertension, grade 3 hypertension in 4.6%. Hypertension is unusual with nintedanib, whether used alone or in combination with chemotherapy [82].

Recently, Reck *et al.* published data from a Phase III trial called LUME-Lung 1. They studied and compared 655 patients treated with docetaxel plus nintedanib versus 659 who received docetaxel plus placebo. These patients were previously treated with one previous chemotherapy regimen for NSCLC, which was histologically or cytologically confirmed stage IIIB/IV recurrent (all histologies). Particularly, data showed that there was a low incidence of cardiovascular side-effects associated with anti-angiogenic agents, such as hypertension or thromboembolism, which have been noted in patients treated with other anti-angiogenic agents in NSCLC. The authors reported some data about asthenia. All-grade asthenia was present in 58 patients among those treated with docetaxel plus nintedanib (8.9%), grade 1 – 2 asthenia was present in 43 patients (6.6%), grade 3 in 13 patients (2.0%), while grade 5 was present in only 2 (0.3%). Chest pain was also reported. All-grade chest pain was present in 56 patients (8.6%), grade 1 – 2 in 46 (7.1%), grade 3 in 4 (0.6%), grade 4 in 3 (0.5%) and grade 5 in 2 patients (0.3%), although it is necessary to underline that asthenia and chest pain are symptoms attributable to various causes [83].

## 6. Expert opinion

Nowadays, the increasing use of anti-angiogenic drugs targeting TKIs enlightened the problem of cardiotoxicity. As emerged from clinical trials, it has a large role in the treatment of cancer patients, namely, for hypertension. It may affect treatment efficacy because of drug interruption. Generally, the incidence and severity of cardiovascular adverse events are related to the underlying cardiovascular risk of the patient. Patients with preexisting hypertension, diabetes, renal disease and prior cardiovascular disease have the highest risk. Hence, optimization of cardiovascular pharmacology is warranted prior to and early in the use of VEGF signaling pathway inhibitors. The role of hypertension as a biomarker for anti-angiogenic drug efficacy is under discussion. Rini *et al.* found

**Table 2. Mean all grades of each side-effect linked to cardiotoxicity of the anti-VEGFR TKIs.**

Drug	Side effect (mean all grades)				
	Hypertension	Cardiac ischemia/infarction	Arterial thromboembolic events	QT prolongation/ECG changes	Congestive heart failure and/or symptoms related (e.g., asthenia, dyspnea)
Sorafenib	~ 11.3%	~ 3.8%	~ 1.7%	~ 40.5%	~ 1%
Sunitinib	~ 34.3%	–	–	–	~ 50%
Pazopanib	~ 35.9%	~ 2%	~ 3%	< 2%	~ 7%
Vandetanib	~ 24.2%	–	–	~ 18%	~ 21%
Axitinib	~ 43%	< 1 %	–	< 1%	21%
Regorafenib	~ 38.3%	–	–	–	6%
Vatalanib	~ 22.7%	–	–	–	~ 22.6%
Nintedanib	15.4%	–	Rare	No clinically significant effect	~ 8.7%

TKIs: Tyrosine kinase inhibitors.

that patients with metastatic RCC treated with sunitinib who developed hypertension had better outcomes. They also observed a low incidence of hypertension-related adverse events. If the possibility of using hypertension as an effective biomarker is interesting, on the other hand, these associations also raise the concern that hypertension treatment may somehow limit the efficacy of TKIs. Based on data from animal models, in which anti-angiogenic drugs were used concomitantly with anti-hypertensive drugs, the treatment of hypertension does not appear to limit antitumor efficacy [16]. Finally, the development of microembolism as an additional cause of cardiac damage cannot be entirely excluded. Therefore, concomitant antithrombotic treatment may be required. This is supported by the findings of myocardial necrosis in the presence of normal coronary arteries, conduction disturbances, which possibly arise from embolism of the atrioventricular nodal artery and the occurrence of non-cardiac vascular events [45]. To date many studies have been conducted to analyze the mechanisms underlying the development of cardiotoxicity, but more should be carried out, aiming to focus on the best cardiology management of this type of toxicity. Oncologists should avoid cancer treatment optimizing cardiologic therapy. For this purpose, new clinical trials should be designed to address cardiac toxicity management. For example, two groups of patients assuming the same anti-angiogenic drug, with different dosages, could be compared for cardiotoxicity incidence. Furthermore, it emerges from some studies that the developing drugs seem to be less cardiotoxic than the older ones, especially as regards nintedanib. The data about hypertension confirm this pattern. On the other hand, although comprehensive data on heart failure are missing, there is information on symptoms related to systolic dysfunction that is quite heterogeneous. A notation should be done about sorafenib because, if on one hand, low percentage of mean all-grade hypertension is registered, on the other hand, it determines a prolongation

of the QT/QTc interval, exposing the patient to an increased risk of ventricular arrhythmias (Table 2).

Anti-angiogenic TKIs should be compared with bevacizumab, which became part of the daily clinical practice. The data from clinical trials, though miscellaneous, suggest that hypertension is induced with bevacizumab in about 30% on average, showing similar values to sunitinib and pazopanib. A negative element for bevacizumab is the incidence of thromboembolic events, which is definitely higher (about 19%) than the incidence registered for anti-angiogenic TKIs, which is very low [84-86].

Some other molecules have been generating interest in the past years, which are selective for VEGFR2 rather than targeting all VEGFR isoforms. The aim of these molecules is to overcome the limitations and especially the side-effects of the previous molecules. Among these drugs, there are small inhibitors that are promising, but data are still limited and information from Phase III trials is lacking. Other molecules generating interest are new monoclonal antibodies that target specifically VEGFR2. Ramucirumab is an example; it is a fully humanized IgG1 monoclonal antibody that blocks the isoform 2 of the receptor. Data from Phase III trials, REGARD and RAINBOW, showed the hypertensive effect of this drug. The frequency of hypertension in the population was similar to the mean value registered for nintedanib (~ 15%) [87-91].

Another important aspect is the monitoring of the development of cardiac adverse events during oncological treatment. The use of predictive biomarkers for cardiotoxicity could play a key role in it. Physicians could benefit from the use of laboratory biomarkers such as TnI, NTproBNP and the analysis of fragments of genetic material such as miRNA.

## Acknowledgment

G Bronte and E Bronte contributed equally to this work.

## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest

in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

## Bibliography

Papers of special note have been highlighted as either of interest (●) or of considerable interest (●●) to readers.

1. Ferrara N, Kerbel RS. Angiogenesis as a therapeutic target. *Nature* 2005;438(7070):967–74
2. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med* 2003;9(6):669–76
- **Important review on VEGF roles and activities, examining its mechanisms in physiological and pathologic conditions and its therapeutic implications.**
3. Goel HL, Mercurio AM. VEGF targets the tumour cell. *Nat Rev Cancer* 2013;13(12):871–82
4. Caraglia M, Santini D, Bronte G, et al. Predicting efficacy and toxicity in the era of targeted therapy: focus on anti-EGFR and anti-VEGF molecules. *Curr Drug Metab* 2011;12(10):944–55
5. Courtney KD, Corcoran RB, Engelman JA. The PI3K pathway as drug target in human cancer. *J Clin Oncol* 2010;28(6):1075–83
6. Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. *Nat Rev Cancer* 2008;8(8):579–91
7. Liu S, Kurzrock R. Toxicity of targeted therapy: implications for response and impact of genetic polymorphisms. *Cancer Treat Rev* 2014;40(7):883–91
8. Liebler DC, Guengerich FP. Elucidating mechanisms of drug-induced toxicity. *Nat Rev Drug Discov* 2005;4(5):410–20
9. Orphanos GS, Ioannidis GN, Ardavanis AG. Cardiotoxicity induced by tyrosine kinase inhibitors. *Acta Oncol* 2009;48(7):964–70
10. Cheng H, Force T. Why do kinase inhibitors cause cardiotoxicity and what can be done about it? *Prog Cardiovasc Dis* 2010;53(2):114–20
11. Hasinoff BB. The cardiotoxicity and myocyte damage caused by small molecule anticancer tyrosine kinase inhibitors is correlated with lack of target specificity. *Toxicol Appl Pharmacol* 2010;244(2):190–5
12. Fabian MA, Biggs WH, Treiber DK, et al. A small molecule-kinase interaction map for clinical kinase inhibitors. *Nat Biotechnol* 2005;23(3):329–36
13. Kerkela R, Woulfe KC, Durand JB, et al. Sunitinib-induced cardiotoxicity is mediated by off-target inhibition of AMP-activated protein kinase. *Clin Transl Sci* 2009;2(1):15–25
14. Hasinoff BB, Patel D, O'Hara KA. Mechanisms of myocyte cytotoxicity induced by the multiple receptor tyrosine kinase inhibitor sunitinib. *Mol Pharmacol* 2008;74(6):1722–8
15. Vaklavas C, Lenihan D, Kurzrock R, Tsimberidou AM. Anti-vascular endothelial growth factor therapies and cardiovascular toxicity: what are the important clinical markers to target? *Oncologist* 2010;15(2):130–41
16. Gupta R, Maitland ML. Sunitinib, hypertension, and heart failure: a model for kinase inhibitor-mediated cardiotoxicity. *Curr Hypertens Rep* 2011;13(6):430–5
17. Henry TD, Annex BH, McKendall GR, et al. The VIVA trial: vascular endothelial growth factor in Ischemia for Vascular Angiogenesis. *Circulation* 2003;107(10):1359–65
- **This study is the first double-blind, placebo-controlled trial evaluating patients treated with rhVEGF. Patients treated with high-dose VEGF had a significant improvement in angina class.**
18. Felmeden DC, Spencer CG, Belgore FM, et al. Endothelial damage and angiogenesis in hypertensive patients: relationship to cardiovascular risk factors and risk factor management. *Am J Hypertens* 2003;16(1):11–20
19. Giordano FJ, Gerber HP, Williams SP, et al. A cardiac myocyte vascular endothelial growth factor paracrine pathway is required to maintain cardiac function. *Proc Natl Acad Sci USA* 2001;98(10):5780–5
20. Chintalgattu V, Ai D, Langley RR, et al. Cardiomyocyte PDGFR-beta signaling is an essential component of the mouse cardiac response to load-induced stress. *J Clin Invest* 2010;120(2):472–84
- **This study proves that platelet-derived growth factor receptor-β signaling plays an important role in cardiomyocyte response to afterload stress, indeed its inhibition impedes cardiac adaptation.**
21. Taimeh Z, Loughran J, Birks EJ, Bolli R. Vascular endothelial growth factor in heart failure. *Nat Rev Cardiol* 2013;10(9):519–30
22. Tao Z, Chen B, Tan X, et al. Coexpression of VEGF and angiopoietin-1 promotes angiogenesis and cardiomyocyte proliferation reduces apoptosis in porcine myocardial infarction (MI) heart. *Proc Natl Acad Sci USA* 2011;108(5):2064–9
23. Kappers MH, de Beer VJ, Zhou Z, et al. Sunitinib-induced systemic vasoconstriction in swine is endothelin mediated and does not involve nitric oxide or oxidative stress. *Hypertension* 2012;59(1):151–7
24. Chintalgattu V, Rees ML, Culver JC, et al. Coronary microvascular pericytes are the cellular target of sunitinib malate-induced cardiotoxicity. *Sci Transl Med* 2013;5(187):187ra69
25. Nachman RL, Rafii S. Platelets, petechiae, and preservation of the vascular wall. *N Engl J Med* 2008;359(12):1261–70
26. Möhle R, Green D, Moore MA, et al. Constitutive production and thrombin-induced release of vascular endothelial growth factor by human megakaryocytes and platelets. *Proc Natl Acad Sci USA* 1997;94(2):663–8
27. Carmeliet P, Lampugnani MG, Moons L, et al. Targeted deficiency or cytosolic truncation of the VE-cadherin gene in mice impairs VEGF-mediated endothelial survival and angiogenesis. *Cell* 1999;98(2):147–57
28. Lampugnani MG, Orsenigo F, Gagliani MC, et al. Vascular endothelial cadherin controls VEGFR-2 internalization and signaling from



- intracellular compartments. *J Cell Biol* 2006;174(4):593–604
29. Shay-Salit A, Shushy M, Wolfvitz E, et al. VEGF receptor 2 and the adherens junction as a mechanical transducer in vascular endothelial cells. *Proc Natl Acad Sci U S A* 2002;99(14):9462–7
  30. Lee S, Chen TT, Barber CL, et al. Autocrine VEGF signaling is required for vascular homeostasis. *Cell* 2007;130(4):691–703
  31. Hasinoff BB, Patel D. Mechanisms of myocyte cytotoxicity induced by the multikinase inhibitor sorafenib. *Cardiovasc Toxicol* 2010;10(1):1–8
  32. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359(4):378–90
  - **This study represents a milestone in the treatment of advanced hepatocellular carcinoma.**
  33. Bronte F, Bronte G, Cusenza S, et al. Targeted therapies in hepatocellular carcinoma. *Curr Med Chem* 2014;21(8):966–74
  34. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol* 2009;27(20):3312–18
  35. Stadler WM, Figlin RA, McDermott DF, et al. Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. *Cancer* 2010;116(5):1272–80
  36. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009;10(1):25–34
  37. Ravaud A, Sire M. Arterial hypertension and clinical benefit of sunitinib, sorafenib and bevacizumab in first and second-line treatment of metastatic renal cell cancer. *Ann Oncol* 2009;20(5):966–7; author reply 67
  38. Choueiri TK, Schutz FA, Je Y, et al. Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. *J Clin Oncol* 2010;28(13):2280–5
  39. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006;368(9544):1329–38
  40. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356(2):115–24
  41. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364(6):501–13
  42. Chen MH, Kerkela R, Force T. Mechanisms of cardiac dysfunction associated with tyrosine kinase inhibitor cancer therapeutics. *Circulation* 2008;118(1):84–95
  43. Rini BI, Cohen DP, LU DR, et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst* 2011;103(9):763–73
  44. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet* 2007;370(9604):2011–19
  45. Schmidinger M, Zielinski CC, Vogl UM, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2008;26(32):5204–12
  46. Hutson TE, Davis ID, Machiels JP, et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2010;28(3):475–80
  47. Davidson BA, Secord AA. Profile of pazopanib and its potential in the treatment of epithelial ovarian cancer. *Int J Womens Health* 2014;6:289–300
  48. Qi WX, Lin F, Sun YJ, et al. Incidence and risk of hypertension with pazopanib in patients with cancer: a meta-analysis. *Cancer Chemother Pharmacol* 2013;71(2):431–9
  49. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010;28(6):1061–8
  50. Pick AM, Nystrom KK. Pazopanib for the treatment of metastatic renal cell carcinoma. *Clin Ther* 2012;34(3):511–20
  51. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012;379(9829):1879–86
  52. Macy ME, DeRyckere D, Gore L. Vandetanib mediates anti-leukemia activity by multiple mechanisms and interacts synergistically with DNA damaging agents. *Invest New Drugs* 2012;30(2):468–79
  53. Grande E, Kreissl MC, Filetti S, et al. Vandetanib in advanced medullary thyroid cancer: review of adverse event management strategies. *Adv Ther* 2013;30(11):945–66
  54. Holden SN, Eckhardt SG, Bassar R, et al. Clinical evaluation of ZD6474, an orally active inhibitor of VEGF and EGF receptor signaling, in patients with solid, malignant tumors. *Ann Oncol* 2005;16(8):1391–7
  55. Force T, Krause DS, Van Etten RA. Molecular mechanisms of cardiotoxicity of tyrosine kinase inhibition. *Nat Rev Cancer* 2007;7(5):332–44
  56. Tamura T, Minami H, Yamada Y, et al. A phase I dose-escalation study of ZD6474 in Japanese patients with solid, malignant tumors. *J Thorac Oncol* 2006;1(9):1002–9
  57. Wells SA, Robinson BG, Gagel RF, et al. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012;30(2):134–41
  58. Leboulleux S, Bastholt L, Krause T, et al. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. *Lancet Oncol* 2012;13(9):897–905
  59. Qi WX, Shen Z, Lin F, et al. Incidence and risk of hypertension with vandetanib in cancer patients: a systematic review and meta-analysis of clinical trials. *Br J Clin Pharmacol* 2013;75(4):919–30
  60. Zang J, Wu S, Tang L, et al. Incidence and risk of QTc interval prolongation among cancer patients treated with vandetanib: a systematic review and meta-analysis. *PLoS One* 2012;7(2):e30353
  61. Verzoni E, Grassi P, Testa I, et al. Targeted treatments in advanced renal

- cell carcinoma: focus on axitinib. *Pharmacogenomics Pers Med* 2014;7:107–16
62. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011;378(9807):1931–9
  63. Rini BI, Schiller JH, Fruehauf JP, et al. Diastolic blood pressure as a biomarker of axitinib efficacy in solid tumors. *Clin Cancer Res* 2011;17(11):3841–9
  64. Qi WX, He AN, Shen Z, Yao Y. Incidence and risk of hypertension with a novel multi-targeted kinase inhibitor axitinib in cancer patients: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2013;76(3):348–57
  65. Hutson TE, Lesovoy V, Al-Shukri S, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. *Lancet Oncol* 2013;14(13):1287–94
  66. Wilhelm SM, Dumas J, Adnane L, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer* 2011;129(1):245–55
  67. FDA approves regorafenib (Stivarga) for GIST. *Oncology (Williston Park)* 2013;27(3):164
  68. FDA approves regorafenib (Stivarga) for metastatic colorectal cancer. *Oncology (Williston Park)* 2012;26(10):896
  69. Rolfo C, Bronte G, Sortino G, et al. The role of targeted therapy for gastrointestinal tumors. *Expert Rev Gastroenterol Hepatol* 2014;8(8):875–85
  70. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013;381(9863):295–302
  71. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013;381(9863):303–12
  72. Bronte G, Rolfo C, Peeters M, Russo A. How to find the Ariadne's thread in the labyrinth of salvage treatment options for metastatic colorectal cancer? *Expert Opin Biol Ther* 2014;14(6):743–8
  73. Kerbel RS. Antiangiogenic therapy: a universal chemosensitization strategy for cancer? *Science* 2006;312(5777):1171–5
  74. Wood JM, Bold G, Buchdunger E, et al. PTK787/ZK 222584, a novel and potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, impairs vascular endothelial growth factor-induced responses and tumor growth after oral administration. *Cancer Res* 2000;60(8):2178–89
  75. Hecht JR, Trarbach T, Hainsworth JD, et al. Randomized, placebo-controlled, phase III study of first-line oxaliplatin-based chemotherapy plus PTK787/ZK 222584, an oral vascular endothelial growth factor receptor inhibitor, in patients with metastatic colorectal adenocarcinoma. *J Clin Oncol* 2011;29(15):1997–2003
  76. Van Cutsem E, Bajetta E, Valle J, et al. Randomized, placebo-controlled, phase III study of oxaliplatin, fluorouracil, and leucovorin with or without PTK787/ZK 222584 in patients with previously treated metastatic colorectal adenocarcinoma. *J Clin Oncol* 2011;29(15):2004–10
  77. Gauler TC, Besse B, Mauguén A, et al. Phase II trial of PTK787/ZK 222584 (vatalanib) administered orally once-daily or in two divided daily doses as second-line monotherapy in relapsed or progressing patients with stage IIIB/IV non-small-cell lung cancer (NSCLC). *Ann Oncol* 2012;23(3):678–87
  78. Dragovich T, Laheru D, Dayyani F, et al. Phase II trial of vatalanib in patients with advanced or metastatic pancreatic adenocarcinoma after first-line gemcitabine therapy (PCRT O4-001). *Cancer Chemother Pharmacol* 2014;74(2):379–87
  79. Eisen T, Shparyk Y, Macleod N, et al. Effect of small angiokinase inhibitor nintedanib (BIBF 1120) on QT interval in patients with previously untreated, advanced renal cell cancer in an open-label, phase II study. *Invest New Drugs* 2013;31(5):1283–93
  80. Rolfo C, Razez LE, Bronte G, et al. BIBF 1120/nintedanib : a new triple angiokinase inhibitor-directed therapy in patients with non-small cell lung cancer. *Expert Opin Investig Drugs* 2013;22(8):1081–8
  81. Doebele RC, Conkling P, Traynor AM, et al. A phase I, open-label dose-escalation study of continuous treatment with BIBF 1120 in combination with paclitaxel and carboplatin as first-line treatment in patients with advanced non-small-cell lung cancer. *Ann Oncol* 2012;23(8):2094–102
  82. Ledermann JA, Hackshaw A, Kaye S, et al. Randomized phase II placebo-controlled trial of maintenance therapy using the oral triple angiokinase inhibitor BIBF 1120 after chemotherapy for relapsed ovarian cancer. *J Clin Oncol* 2011;29(28):3798–804
  83. Reck M, Kaiser R, Mellemaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol* 2014;15(2):143–55
  84. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350(23):2335–42
  85. Abdel-Rahman O, Fouad M. Bevacizumab-based combination therapy for advanced gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs): a systematic review of the literature. *J Cancer Res Clin Oncol* 2014. In press
  86. Kümler I, Christiansen OG, Nielsen DL. A systematic review of bevacizumab efficacy in breast cancer. *Cancer Treat Rev* 2014;40(8):960–73
  87. Xia Y, Song X, Li D, et al. YLT192, a novel, orally active bioavailable inhibitor of VEGFR2 signaling with potent antiangiogenic activity and antitumor efficacy in preclinical models. *Sci Rep* 2014;4:6031
  88. Tian S, Quan H, Xie C, et al. YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity in vitro and in vivo. *Cancer Sci* 2011;102(7):1374–80
  89. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or

gastro-oesophageal junction  
adenocarcinoma (REGARD):  
an international, randomised,  
multicentre, placebo-controlled,  
phase 3 trial. *Lancet*  
2014;383(9911):31–9

90. Wilke H, Muro K, Van Cutsem E, et al.  
Ramucirumab plus paclitaxel versus  
placebo plus paclitaxel in patients with  
previously treated advanced gastric or  
gastro-oesophageal junction  
adenocarcinoma (RAINBOW): a double-  
blind, randomised phase 3 trial.  
*Lancet Oncol* 2014;15(11):1224–35
91. Bronte G, Galvano A, Cicero G, et al.  
Ramucirumab and its use in gastric  
cancer treatment. *Drugs Today (Barc)*  
2014;50(9):613–21

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